An epidemiologic health study of Manganese exposure in East Liverpool

RATIONALE FOR STUDY

A current draft health consultation by ATSDR (to be released shortly) will evaluate potential health risks from ambient metals measures, including manganese, in East Liverpool, Ohio, a small town on the Ohio river. Ambient air monitors in East Liverpool have shown high levels of metals over the past 10 years. The purpose of this monitoring was to determine which metals exceeded the respective reference concentrations. It was determined that ambient air levels of Mn and chrome were elevated, which suggested the need for a health risks assessment. Ohio EPA identified as a source the S.H. Bell Company, which stores and packages primarily raw metals from all over the world. Because the Mn air levels in East Liverpool are 50 times higher than those of a current health study conducted in 2 similarly-sized towns in Ohio, it seems highly important to a) study the health risks to residents of this higher Mn exposure in East Liverpool and b) to compare these health effects to the towns currently being studied by a team of investigators with experience in the health effects of Mn in adults.

There is a time urgency to perform a health study of the potential Mn health risks in East Liverpool because the S.H. Bell Company has been required by Ohio EPA to reduce their emissions by November 2010. This points to the need to conduct a study within a short timeframe. The expert research team proposing this health evaluation is prepared to conduct such a study of East Liverpool on short notice, because they have already developed their epidemiologic methods and applied them in a present health study of the nearby Mn exposed town of Marietta, Ohio. Relevant health questionnaires, which include questions on demographic and residential history, symptoms and illnesses, environmental risk characteristics, such as intake of Mn and iron in diet, time spent indoors and outdoors, have already been developed and tested and are appropriate for use in East Liverpool. Additionally, the expert collaborators, trained neuropsychological testers, medical experts, and statisticians who are collaborating on the Marietta study are available and willing to assist in a new proposed health study project in East Liverpool.

BACKGROUND

Air monitoring in three locations near the S.H. Bell Company in East Liverpool has already been conducted by the Ohio EPA and the ATSDR over a period of 10 years. The S.H. Bell Company handles a great volume of raw and processed metal products. S.H. Bell has two locations in East Liverpool

approximately 1 mile apart: the Little England facility and the State Line facility. At both locations, ferrous and nonferrous materials are stored, transferred, and warehoused. S.H. Bell Company is equipped to process, dry, crush, screen, and package their materials for industry. Shipping occurs through river barge, truck, and rail.

This proposed project is to be conducted with a randomly selected sample of adult residents aged 30-75 years (under separate funding with partial in-kind contributions of personnel from the ATSDR and EPA). Randomly selected study participants will include 100 residents, selected from property tax and water records in East Liverpool, OH, within a parameter of 5 miles from the S.H. Bell Company. This study will include neurological testing, neuropsychological evaluations, and measures of Mn exposure data in air with Mn biomarkers measured in blood and hair. Upon completion, this study will contribute knowledge on the potential risk for health effects associated with the higher ambient Mn air measured in East Liverpool.

East Liverpool has 13,089 residents and is similar in size to the two towns (Marietta 14,515 and Mt. Vernon 14,375) currently being studied by the investigators. East Liverpool is also similar to these two towns in ethnic and gender proportions, median age, and income; however, the percentage of residents living below poverty in East Liverpool is lower than in Marietta and Mt. Vernon. The percent of residents having graduated from high school in East Liverpool (73%) is higher than in Marietta (34%) and Mt. Vernon (39%) but fewer residents are college graduates or have post-graduate degrees. Both Mn exposed towns, Marietta and East Liverpool, are situated on the Ohio river and both have industries near the city. Both Marietta and East Liverpool have industrial plants with documented chemical emissions, with Mn being the pollutant of greatest concern. Mn exposure for Mt. Vernon was considered to be low based on data from the Toxic Release Inventory, and the town was therefore selected as a control town. The exposed town of Marietta has an industrial complex with a ferroalloys facility, Eramet, being the main point source for Mn emissions. Mn air emissions in Marietta have been shown to range from 0.01 to a maximum concentration of 0.5 $\mu g/m^3$; while East Liverpool, the proposed more highly exposed town, has Mn maximum concentrations of 25.0 ug/m^3, which is 50 times higher than in Marietta.

PRELIMINARY RESULTS of the Marietta and Mt. Vernon study

Preliminary data of the Marietta health study suggest that Mn in blood in Marietta (mean = 9.65, *sd* = 3.21, range = 4.91-24.6) did not differ from Mn in blood in the control town of Mt. Vernon (mean = 9.48, *sd* = 3.16, range = 3.75 – 18.9). Neurological and neuropsychological function also did not differ between

the towns. Residents from the two towns score in the average range of normative data reported by the test publishers.

Proposed STUDY PLAN

One-hundred participants between the ages of 30-75 years will be recruited at random in East Liverpool. Exclusion criteria will include having had other chemical exposures, less than ten years of residence, and having had any major illnesses that would affect neurological and/or neuropsychological function. To avoid possible groundwater contamination, only those residents on municipal water supply will be eligible to participate. Data collected will be kept strictly confidential and will be identified by ID numbers only. Approval from both the Institutional Review Boards of San Francisco State University and the Ohio Department of Health, which have already approved these methods used in the Marietta health study, will be obtained before any testing takes place.

If funded, testing would be conducted in the town of East Liverpool in early 2011. All collaborators who worked on earlier study, including Dr. Roels who was responsible for setting up the temporary laboratory and Dr. Kim, who administered the Unified Parkinson's Disease Rating Scale (UPDRS), have agreed to volunteer professional time (expenses will be paid) so that the methods and testers will be identical to the initial project. Blood analyses will again be carried out by the CDC Laboratory for Mn, Cd, Pb, and Hg. Hair analyses will be done by a laboratory who has a suitable methodology of preparing and analyzing hair. Serum analyses of ferritin, a potential confounder competing with Mn for the same transport system to the brain, will be completed at the U.S. EPA Laboratory. Ms. Stephanie Davis of the ATSDR will give assistance to Ms. Jaime Wagner of U.S. EPA, Region 5, who will model the Mn air exposure grids in the exposed town of East Liverpool.

STATISTICAL PLAN

In order to compare scores on neuropsychological and motor tests and UPDRS scores between the 3 towns, the multivariate general linear model will be used. This will test for differences between participants in the three towns, including pair wise comparisons for differences in domains of neurological and neuropsychological and motor functioning. Logistic regressions will be used for categorical outcomes such as symptom and illness frequencies in relation to modeled Mn air exposure, comparing the relative risk between the samples.

Multiple regression analyses will test for relationships between Mn levels in air and neuropsychological test scores in East Liverpool, and these relationships will be compared to those recently found in Marietta. Logistic regressions will be used for categorical outcomes to examine the relationship between Mn levels in air and risk for particular illnesses or symptoms. Power analyses have indicated that the study will have sufficient power to answer the research questions.

The following will occur: 1) recruit a study population in East Liverpool, with the aid of ATSDR and U.S. EPA Region 5, who have already performed an exposure assessment of Mn in ambient air concentrations and 2) assess associations with ambient airborne and dietary sources of manganese, performance on a neuropsychological test battery, and self-reported respiratory and other symptoms of concern in the community.

The results from this study will determine if differences in manganese body burden can be discriminated within and between the samples of approximately 290 participants from the three communities and what health outcomes and risk factors are associated with airborne Mn, and Mn in blood, hair and serum (adjusted for ferritin levels in serum). The opportunity of conducting the study in East Liverpool should help us to widen the exposure range (Mn-air) and be useful to test the hypothesis whether the newly proposed MRL of ATSDR of 0.3 $\mu g/m^3$ is justified or whether a higher RfC would be possible, as suggested in the Bailey et al. paper. (RfC of 2 $\mu g/m^3$ derived from a NOAEL or 7 $\mu g/m^3$ derived from a BMDL10).

The study protocol for East Liverpool will address the following research questions.

1. Are the modeled ambient air concentrations for East Liverpool residents significantly higher than those in Marietta?
2. Are blood, hair and serum, Mn levels significantly elevated in the adult residents of East Liverpool than of the 2 comparison communities?
3. What is the gradient of Mn body burden for each of 3 communities (mean, median, standard deviation, and range)?
4. What differences in environmental and lifestyle factors may contribute to blood and hair Mn levels in residents living in each of the 3 towns?
5. Is Mn body burden associated with neurological or neuropsychological function or medical symptoms and illnesses?
6. Is the prevalence of these outcomes different between the 3 towns?
7. Is a geographic gradient of the above health outcomes for the East Liverpool community consistent with modeled estimates of airborne Mn concentration?

INVESTIGATORS AND EXAMINERS

- San Francisco State University
  Dr. Rosemarie Bowler
- Université Catholique de Louvain (UCL), Brussels, Belgium
  Dr. Harry Roels

- Department of Occupational and Environmental Medicine, Ulsan University Hospital, College of Medicine, South Korea
  Dr. Yangho Kim
- Department of Medicine, Beth Israel Deaconess Medical Center Harvard Medical School, Boston, Massachusetts
  Dr. Long Ngo

Trained examiners/psychometricians:

Vihra Gocheva, MA (pending at San Francisco State University)

Matthew Harris, MA, PhD (pending at Alliant International University, San Francisco, CA)

Katherine Wilson, MA, PhD (pending at Alliant International University, San Francisco, CA)

Nadia Abdelouhab, Ph.D., University of Sherbrook, Montreal, Canada

Linda Mora, MA, PhD (pending at Pacific Graduate School of Psychology, Palo Alto, CA)

2 trained SFSU Graduate Psychology students, TBA from 2 B.A. level students from SFSU who have worked on the project since its beginning in 2009

1-2 additional trained data-entry persons from research psychology classes at SFSU.

Appendix: Budget (May 4, 2010)

Testers (n=6+ 1)			Total
	Days	Pay rate ($/day)	
Pay	3	200	$3,600
Per diem	3	40	$720
Catsys examiner	3	200	$600
Catsys exam (per diem)	3	40	$120
		subtotal	**$5,040**
Staff (n = 2)			
Pay	3	100	$600
Per diem	3	40	$240
		subtotal	**$840**
P.I.			
Pay	3	250	$750
Per diem	3	40	$120
		subtotal	**$870**
TRAVEL (Domestic)			
	people	airfare	
	10	500	$5,000
		subtotal	**$5,000**
TRAVEL (International)			
	people	airfare	
	2	1100	$2,200
		subtotal	**$2,200**
International Collaborators (n=2)			
	days		
per diem	3	40	$240
		subtotal	**$240**
Car rental (n=3)			
	days	rate ($/day)	
rental	5	80	$1,200
gasoline		40	$120
		subtotal	**$1,320**
Lodging (n = 7)			
	nights	rate ($/day)	
	4	80	$2,240
conference room	3	80	$240

		subtotal	**$2,480**
Participant Stipends			
	people	amount	
	100	50	$5,000
		subtotal	**$5,000**
Biomarker Analyses			
	n		
Mn B	100	52	$5,200
Mn Hair	100	32	$3,200
		subtotal	**$8,400**
Supplies		amount	
test protocols		**800**	**$800**
postage and supplies		400	$400
telephone and fax		200	$200
		subtotal	**$1,400**
Salaries			
	months	payrate ($/month)	
PI	6	1000	$6,000
Manager	6	1000	$6,000
Assistant	6	1000	$6,000
Senior Statistical Consultant		3000	$3,000
Statistician	6	1000	$6,000
	hours	payrate ($/hour)	
Student Assistant 1	200	12	$2,400
Student Assistant 2	200	12	$2,400
Student Assistant 3	200	12	$2,400
Student Assistant 4	200	12	$2,400
		subtotal	**$36,600**
		TOTAL	**$69,390**